

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 209/12, A61K 31/395, C07D 215/14, 405/04, 413/12, 215/08, 401/12, 413/06		A1	(11) International Publication Number: WO 00/15612 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/GB99/02819 (22) International Filing Date: 26 August 1999 (26.08.99) (30) Priority Data: 9818641.4 26 August 1998 (26.08.98) GB 60/110,008 25 November 1998 (25.11.98) US (71) Applicant (for all designated States except US): RHONE-POULENC RORER LIMITED [GB/GB]; RPR House, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4AH (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BOURZAT, Jean-Dominique [FR/FR]; Rhône-Poulenc Rorer Recherche Developpement, Centre de Recherche de Vitry-Alfortville, 13, quai Jules Guesde, BP14, F-94403 Vitry Sur Seine Cedex (FR). COMMERCON, Alain [FR/FR]; Rhône-Poulenc Rorer Recherche Developpement, Centre de Recherche de Vitry-Alfortville, 13 quai Jules Guesde, BP14, F-94403 Vitry Sur Seine Cédex (FR). FILOCHE, Bruno, Jacques, Christophe [FR/FR]; Rhône-Poulenc Rorer Recherche Developpement, Centre de Recherche de Vitry-Alfortville, 13 quai Jules Guesde, BP14, F-		94403 Vitry Sur Seine Cedex (FR). HARRIS, Neil, Victor [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). McCARTHY, Clive [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). (74) Agent: LEE CAFFIN; Rhone-Poulenc Rorer Limited, Patent Department, Rainham Road South, Dagenham, Essex RM10 7xs (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. With amended claims.	
(54) Title: AZA-BICYCLES WHICH MODULATE THE INHIBITION OF CELL ADHESION			
<p style="text-align: center;">(I)</p>			
(57) Abstract			
<p>The invention is directed to physiologically active compounds of formula (I) wherein R¹ represents R³-Z³-, R³-L²-R⁴-Z³-, R³-L³-Ar¹-L⁴-Z³- or R³-L³-Ar¹-L²-R⁴-Z³-; R² represents hydrogen, halogen, lower alkyl or lower alkoxy; A¹ represents a straight chain C₁-3alkylene linkage optionally substituted by one or more groups chosen from alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, imino, oxo, thioxo, or alkyl substituted by -ZR⁶, -NY¹Y², -CO₂R⁶ or -C(=O)-NY¹Y²; L¹ represents a direct bond; an alkenylene, alkylene, alkynylene, cycloalkenylene, cycloalkylene, heteroaryldiyl, heterocycloalkylene or arylene linkage each optionally substituted by (a) an acidic functional group, cyano, oxo, -S(O)_mR⁹, R³, -C(=O)-R³, -C(=O)-OR³, -N(R⁸)-C(=O)-R⁹, -N(R⁸)-C(=O)-OR⁹, -N(R⁸)-SO₂-R⁹, -NY⁴Y⁵ or -[C(=O)-N(R¹⁰)-C(R⁵)(R¹¹)]_p-C(=O)-NY⁴Y⁵, or by (b) alkyl substituted by an acidic functional group, or by S(O)_mR⁹, -C(=O)-NY⁴Y⁵ or -NY⁴Y⁵; a -[C(=O)-N(R¹⁰)-C(R⁵)(R¹¹)]_p- linkage; a -Z²-R¹²- linkage; a -C(=O)-CH₂-C(=O)- linkage; a -R¹²-Z²-R¹²- linkage; a -C(R⁴)(R¹³)-[C(=O)-N(R¹⁰)-C(R⁵)(R¹¹)]_p- linkage; or a -L⁵-L⁶-L⁷- linkage; Z¹ is C(R⁷)(R^{8a}), C(=O) or CH(OH); Y is carboxy or an acid bioisostere; and the corresponding N-oxides, and their prodrugs; and pharmaceutically acceptable salts and solvates of such compounds and their N-oxides and prodrugs. Such compounds have valuable pharmaceutical properties, in particular the ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4 (α4β1).</p>			

BEST AVAILABLE COPY